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Epidemiology and burden of rotavirus disease in Central Asia

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SUMMARY

Background: Rotavirus infection is the most common cause of severe gastroenteritis in children worldwide. New rotavirus vaccines are not currently used in the five countries that make up the Central Asian region. Three of these countries, Kazakhstan, Uzbekistan, and Kyrgyzstan, have a combined total population of 48 million and an estimated 1 million annual births.

Methods: We conducted prospective hospital-based surveillance for rotavirus diarrhea in three Central Asian countries (Kazakhstan, Uzbekistan, and Kyrgyzstan) during 2005–2009 to estimate the burden of rotavirus. We calculated the proportion of rotavirus among children aged <5 years hospitalized with acute diarrhea and estimated numbers of rotavirus-associated deaths, hospitalizations, outpatient visits, and home care episodes.

Results: Of 20 780 children hospitalized with diarrhea and enrolled in the study, 26% (95% confidence interval (CI) 25–27) were positive for rotavirus antigen by ELISA. On an annual basis, 4007 (2.6 per 1000 child-years) rotavirus hospitalizations occur in Kazakhstan, 5491 (2.1 per 1000 child-years) in Uzbekistan, and 3883 (6.8 per 1000 child-years) in Kyrgyzstan. Rotavirus is also estimated to cause 68 (0.04 per 1000 child-years) deaths in children aged <5 years in Kazakhstan, 662 (0.25 per 1000 child-years) in Uzbekistan, and 156 (0.27 per 1000 child-years) in Kyrgyzstan.

Conclusion: This study presents an epidemiological picture of rotavirus disease in Central Asia and illustrates a substantial rotavirus burden, which is preventable with rotavirus vaccination.

1. Introduction

Rotavirus is the leading cause of severe childhood gastroenteritis in both developed and developing countries.[1,2] An estimated 2.3 million hospitalizations and approximately 527 000 deaths in children aged <5 years are caused by rotavirus[3] annually worldwide, but most rotavirus-associated deaths occur in low-income countries.[2] Approximately 95% of children are infected before 3–5 years of age, and the highest incidence occurs between 6 and 24 months of age.[4] Rotavirus can also affect adults and is often manifested in subclinical forms.[5]

The possibility of an effective prevention of rotavirus infection through improvements in hygiene and sanitary conditions is limited.[6–8] Vaccination is the most effective method for preventing rotavirus infection, and two licensed rotavirus vaccines have been available on the world market since 2006.[9] Their efficacy and safety have been demonstrated in large-scale clinical trials, although efficacy estimates for these vaccines have differed between industrialized and developing countries. In Europe, the efficacy against severe rotavirus diarrhea reached 90–98%,[10,11] whereas studies conducted in several African and Asian countries demonstrated an overall efficacy of 39.3%[12] and 48.3%,[13] respectively. At present, several countries have already introduced the rotavirus vaccine into routine practice, and data on the effectiveness of vaccines differ in developed and developing countries. Thus, the effectiveness against severe disease was 86–94% in the USA[14] and 74% Austria,[15] but data from Nicaragua demonstrate an effectiveness of 58% against severe cases and 77% against very severe disease.[16] There are multiple explanatory reasons for the lower efficacy of rotavirus vaccines in the developing countries of

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Africa[12] and Asia,[13] including young age at vaccination, high levels of maternal antibodies, co-administration with oral poliovirus vaccine, breastfeeding, poorer nutritional status, and presence of other enteric microorganisms in a child's gut. Despite the lower efficacy in developing settings, the introduction of new rotavirus vaccines into routine immunization in these settings may decrease the rates of morbidity and mortality from diarrhea. Thus, the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization have recommended the inclusion of rotavirus vaccines into national immunization programs globally,[17] and national policymakers need to decide whether to introduce such a program. This decision must be based on local information about rotavirus-specific mortality and morbidity. Such information is available in several developing countries, but knowledge about the epidemiology and burden of rotavirus infection in the Central Asian region is still lacking. The five Central Asian countries (Kazakhstan, Kyrgyzstan, Uzbekistan, Turkmenistan, and Tajikistan) are highly populated and have a warm and dry climate with a shortage of water resources. Diarrheal disease is an important public health problem, and is estimated to cause between 2% and 14% of deaths among children under 5 years of age.[18]

We conducted our study in three Central Asian republics: Kazakhstan, Kyrgyzstan, and Uzbekistan. These are newly independent states with a combined population of 48 million and an estimated 1 million annual births. The under-5 mortality rate varies by country, but is estimated to be between 30 and 38 deaths per 1000 live-births.[19–21] Because of a common Soviet heritage, all three countries have similar health care systems, though due to different rates of economic development, Uzbekistan and Kyrgyzstan are classified by the World Bank as low-income countries (USD 910 and USD 780 gross national income (GNI) per capita, respectively), whereas Kazakhstan is an upper-middle income economy (USD 6160 GNI per capita) (Table 1).[22] Based on their GNI, Uzbekistan and Kyrgyzstan are eligible for new vaccine assistance from the GAVI Alliance, which only supports countries with a GNI per capita below USD 1000.[23]

Knowing that routine childhood immunizations in these countries are provided through the centrally managed national program and that there is high vaccine coverage (coverage for the third dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine (DTP3) at 1 year of age is 96–99%),[24,25] it is possible that rotavirus vaccination could be an effective tool in preventing rotavirus infection in these settings. Hospital-based rotavirus surveillance was initiated in Uzbekistan and Kyrgyzstan in 2005, and the initial assessments of rotavirus burden in these countries have been published.[26,27] In Kazakhstan, however, similar surveillance started in late 2007. This study presents new 2-year data from Kazakhstan and reviewed and updated data from Kyrgyzstan and Uzbekistan for the period 2007–2009. We describe country-specific results and present the burden of rotavirus disease from a regional perspective in order to help the national and regional decision-making on the introduction of rotavirus vaccine.

Table 1
Main characteristics of the three Central Asian republics included in the study

Country	GNI per capita, USD[a]	Population, millions[b]	Birth cohort, thousands[c]	Under-5 mortality rate[c]
Kazakhstan	6140	15.7	349	30.2
Uzbekistan	910	27.3	553	38.0
Kyrgyzstan	740	5.2	120	38.4

GNI, gross national income; USD, US dollars.
[a] The World Bank country data 2010; available at: http://data.worldbank.org/.
[b] World Health Organization Statistical Information System (WHOSIS); available at: http://www.who.int/whosis/en/.
[c] UNICEF.[19–21]

2. Methods

2.1. Sentinel sites and study period

We used an identical study protocol in all countries, which was developed in accordance with the WHO's generic protocol for rotavirus hospital-based surveillance.[28] In each country, we chose two sentinel infectious diseases hospitals admitting children with acute gastroenteritis. In Central Asia, health care systems are quite similar across countries, with all children with diarrhea being exclusively treated in infectious disease hospitals. In urban areas, children are treated in city hospitals for infectious diseases, whereas children from semi-urban or rural areas are admitted to regional or district hospitals for infectious diseases. This hierarchy of hospitals for diarrhea patients is similar across the study countries, and in order to increase comparability of data across countries, sentinel sites were chosen to represent urban and semi-urban/rural areas).

2.2. Case definition and sampling

The case definition and inclusion/exclusion criteria were based on the WHO's generic protocol for rotavirus hospital-based surveillance.[28] All children <5 years of age with acute gastroenteritis admitted to participating hospitals within 7 days of onset were eligible for the study. Acute gastroenteritis was defined by the physician who admitted the child for hospitalization. Children with other acute co-morbidities or chronic diarrhea were excluded in each country, while every third eligible child was enrolled in an urban hospital and every second one in a hospital located in a semi-urban/rural area. Data collected from each child included information on the patient's age, admission and discharge dates, and duration of symptoms. Written informed consent was obtained from the parent(s) of each enrolled patient.

2.3. Sample collection and testing

Stool samples were obtained from each enrolled child within 24 h after admission to hospital and were kept at 4 °C prior to ELISA testing. In Kazakhstan, samples were processed and stored in the Department of Virology of the Republican Center for State Sanitary and Epidemiological Control in Almaty and in the Virology Laboratory of Infectious Diseases in Karaganda. For rotavirus detection, we used commercial ELISA assays: RIDASCREEN® Rotavirus (R-Biopharm, Darmstadt, Germany) in Kazakhstan and DAKO IDEIA Rotavirus (DAKO Diagnostics Ltd, Glostrup, Denmark) in Uzbekistan and Kyrgyzstan. Diagnostic and stool sample processing procedures were the same in all countries and are described in detail elsewhere.[26,27]

2.4. Data management and analysis

All collected data were entered into an electronic database. Characteristics of the rotavirus-positive and rotavirus-negative patients and differences between countries were compared using the Chi-square test and *t*-test. To estimate the cumulative risk of rotavirus-associated hospitalizations and deaths, we applied surveillance data to the nationally reported number of gastroenteritis hospitalizations and to WHO diarrhea-specific mortality estimates in children <5 years of age.[19–21] The WHO's diarrhea estimates were used because national diarrhea-specific mortality rates were not available. Due to a lack of data about outpatient (polyclinic) visits and number of mild (home care) cases, the

Table 2
Number of enrolled children under 5 years of age with acute gastroenteritis hospitalized in sentinel hospitals, and proportion of rotavirus-positive cases

Year	Kyrgyzstan		Uzbekistan		Kazakhstan		Total number	
	No. enrolled	% RV positive (95% CI)	No. enrolled	% RV positive (95% CI)	No. enrolled	% RV positive (95% CI)	No. enrolled	% RV positive (95% CI)
2005	1021	24 (21–27)	1597	33 (31–36)			2618	30 (28–31)
2006	1989	26 (24–28)	1940	26 (25–28)			3929	26 (25–28)
2007	746	26 (23–30)[a]	1809	24 (22–26)[b]	110	29 (20–38)[c]	2665	25 (23–27)
2008	1882	21 (19–23)	2286	26 (24–28)[b]	1763	33 (31–35)	5931	26 (25–27)
2009	1810	25 (23–27)	2534	22 (20–24)	1293	26 (24–29)	5637	24 (23–25)
Total	7448	24 (23–25)	10 166	26 (25–27)	3166	30 (28–32)	20 780	26 (25–27)

RV, rotavirus; CI, confidence interval.
[a] Data do not include period from June to July 2008.
[b] Data do not include period from December 2007 to May 2008.
[c] Data presented only for December 2007.

number of outpatient visits and the number of mild cases were estimated on the basis of the approach described by Parashar et al.[1] Based on this, we assumed that for every hospitalized rotavirus case, there are 8 (range 5–10) outpatient visits associated with rotavirus diarrhea, and for each case requiring outpatient (polyclinic) care, there are 4 (range 3–5) mild cases of rotavirus diarrhea requiring home care only.

3. Results

3.1. Hospital surveillance

A total of 20 780 hospitalized children with acute gastroenteritis in all three countries during the surveillance period were enrolled in the study. Of these, 10 166 (49%) were enrolled in Uzbekistan, 7448 (36%) in Kyrgyzstan, and 3166 (15%) in Kazakhstan. Stool samples were obtained from all enrolled children, and 5398 (26%, 95% confidence interval (CI) 25–27) were rotavirus-positive by ELISA (Table 2). The overall proportions of rotavirus-positive cases did not differ substantially between countries, with 24% (95% CI 23–25) detected in Kyrgyzstan, 26% (95% CI 25–27) in Uzbekistan, and 30% (95% CI 28–32) in Kazakhstan. Nevertheless, these slight differences in detection rates between countries were still statistically significant ($p < 0.05$) due to a large number of observations. However, annual detection rates fluctuated over the study period in Kyrgyzstan and Kazakhstan, although these fluctuations were within the 95% CI. In Uzbekistan, the rotavirus detection rate slightly decreased over a 5-year period from 33% (95% CI 31–36) to 22% (95% CI 20–24), which may have been related to sampling errors.

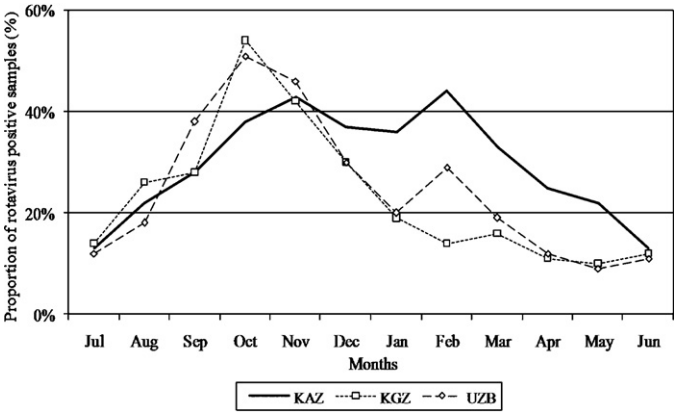

Figure 1. Percentage of rotavirus-positive cases by month in children aged <5 years in three Central Asian republics (KAZ, Kazakhstan; UZB, Uzbekistan; KGZ, Kyrgyzstan), 2005–2009 (*aggregate data for 2005–2009 presented for UZB and KGZ, and 2008–2009 data presented for KAZ).

The mean age of rotavirus-positive cases was 14.1 months (standard deviation (SD) 9.9) for all children in the three countries (Table 3). The lowest mean age was detected in Kyrgyzstan (12.5, SD 8.9) and the highest in Uzbekistan (15.2, SD 10.4). Rotavirus was detected in children of all age groups, but those under 2 years of age accounted for 86.2% of all cases (Table 3). About half (48.4%) of the hospitalized children with rotavirus diarrhea were below the age of 1 year. No significant differences in the proportion of children <1 year old were found between the countries.

Table 3
Characteristics of rotavirus-positive children under 5 years of age with acute gastroenteritis hospitalized in sentinel hospitals

Characteristic	Kyrgyzstan (n=1815)	Uzbekistan (n=2632)	Kazakhstan (n=951)	Total number (n=5398)	p-Value of difference[a]
Age groups, months, n (%)					
0–2	98 (5.4)	74 (2.8)	67 (7.0)	239 (4.4)	$p<0.0001$
3–5	210 (11.6)	242 (9.2)	105 (11.0)	557 (10.3)	
6–11	699 (38.5)	824 (31.3)	292 (30.7)	1815 (33.6)	
12–23	643 (35.4)	1048 (39.8)	349 (36.7)	2040 (37.8)	
24–35	103 (5.7)	266 (10.1)	96 (10.1)	465 (8.6)	
36–47	40 (2.2)	136 (5.2)	29 (3.0)	205 (3.8)	
48–59	22 (1.2)	42 (1.6)	13 (1.4)	77 (1.4)	
Mean age, months (SD)	12.5 (8.9)	15.2 (10.4)	13.9 (10.2)	14.1 (9.9)	$p<0.0001$
Sex					
Male, n (%)	1040 (57.3)	1517 (57.6)	550 (57.8)	3107 (57.6)	$p>0.05$
Frequency of					
Fever, n (%)	1290 (71.1)	2358 (89.6)	823 (86.5)	4471 (82.8)	$p<0.0001$
Vomiting, n (%)	989 (54.5)	1991 (75.6)	787 (82.8)	3767 (69.8)	$p<0.0001$
Mean hospitalization duration, days (SD)	4.9 (1.9)	5.8 (2.1)	5.3 (2.1)	5.6 (2.1)	$p>0.05$

SD, standard deviation.
[a] p-Value of the difference by t-test or Chi-square test.

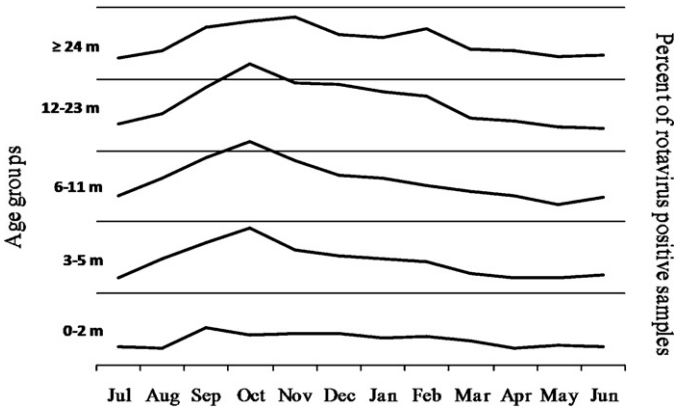

Figure 2. Percentage of rotavirus-positive cases by age and by month in children aged <5 years in three Central Asian republics, 2005–2009 (*aggregate data for all three countries (Uzbekistan, Kazakhstan, and Kyrgyzstan) presented; **aggregate data for 2005–2009 presented for Uzbekistan and Kyrgyzstan, and 2008–2009 data presented for Kazakhstan).

Rotavirus was observed year-round in all countries, but infections were more common from October through March. The major peak was detected during October–November in all three countries, followed by a second peak in February that was only observed in Uzbekistan and Kazakhstan (Figure 1). This seasonality pattern became more pronounced with increasing age (Figure 2), with the second peak being observed more among children aged 24 months and older. We did not find a clear statistical association between the second peak and other possible confounders such as gender or site.

In all rotavirus-positive patients, a fever was detected in 4471 (82.8%) and vomiting in 3767 (69.8%) children. Interestingly, the frequency of fever and vomiting was the lowest in Kyrgyzstan (71.1% and 54.5%, respectively) among all countries, suggesting that cases with milder forms of diarrhea may have been hospitalized there more frequently.

3.2. Disease burden

According to the ministries of health of each country, the total registered number of gastroenteritis hospitalizations in children <5 years was 13 357 in Kazakhstan, 21 120 in Uzbekistan, and 16 178 in Kyrgyzstan in 2009. By applying the rotavirus proportion from the surveillance data of each country, we estimated 4007 (2.6 per 1000 child-years) annual rotavirus hospitalizations in Kazakhstan, 5491 (2.1 per 1000 child-years) in Uzbekistan, and 3883 (6.8 per 1000 child-years) in Kyrgyzstan (Table 4). This corresponds to one in every 87 children in Kazakhstan, one in every 101 in Uzbekistan, and one in every 31 in Kyrgyzstan being hospitalized for rotavirus gastroenteritis by the age of 5 years. In total, we estimated 13 381 (2.8 per 1000 child-years) hospitalizations that are attributable to rotavirus in the three countries combined, which suggests that one in every 82 children in the region is hospitalized for rotavirus gastroenteritis by age 5.

Since the proportion of diarrhea-associated deaths dropped dramatically in these countries recently (from 16.5% in 2004 to 2% in 2008 in Kazakhstan, from 22.3% to 12% in Uzbekistan, and from 19.9% to 14% in Kyrgyzstan[29]), we used the latest available international estimates of under-5 deaths in each country to calculate rotavirus-attributable deaths. By applying the WHO's proportion of under-5 deaths attributable to diarrhea,[29] we estimated that rotavirus caused 68 (0.04 per 1000 child-years) deaths annually in children <5 years in Kazakhstan, 156 (0.27 per 1000 child-years) in Kyrgyzstan, and 662 (0.25 per 1000 child-years) in Uzbekistan (Table 4). This translates to a risk of one in 5132, 769, and 835 children dying from rotavirus before 5 years of age in Kazakhstan, Kyrgyzstan, and Uzbekistan, respectively. In total, 886 child deaths each year are attributable to rotavirus in these three Central Asian republics, suggesting that one child in approximately 1153 dies from rotavirus before 5 years of age in the region. These estimates of rotavirus-related mortality are considerably lower than previously reported.[26,27]

Because no country-specific data on outpatient visits or home care episodes of acute gastroenteritis among children aged <5 years were available, we estimated these events using a previously described approach.[30] Based on this approach, 32 506 annual rotavirus outpatient clinic visits were calculated to occur in Kazakhstan, 43 928 in Uzbekistan, and 31 064 in Kyrgyzstan, amounting to 107 498 outpatient clinic visits per year. The number of mild (home care) cases of rotavirus diarrhea was estimated at 130 024, 175 712, and 124 256 annually in Kazakhstan, Uzbekistan, and Kyrgyzstan, respectively, suggesting that 429 992 mild cases may occur each year in the three Central Asian republics. In other

Table 4
Rotavirus disease burden among children under 5 years of age in three Central Asian republics, 2009

	Kazakhstan	Kyrgyzstan	Uzbekistan	Total
RV deaths[a]				
n, thousands (range)	0.068 (0.063–0.072)	0.156 (0.150–0.163)	0.662 (0.637–0.688)	0.886 (0.850–0.923)
Incidence rate[b]	0.04	0.27	0.25	0.18
Cumulative risk[c]	1:5132	1:769	1:835	1:1153
RV hospitalizations[d]				
n, thousands (range)	4.0 (3.7–4.3)	3.9 (3.7–4.0)	5.5 (5.3–5.7)	13.4 (12.9–13.8)
Incidence rate[b]	2.6	6.8	2.1	2.8
Cumulative risk[c]	1:87	1:31	1:101	1:82
RV outpatient clinic visits[e]				
n, thousands (range)	32.5 (18.7–42.7)	31.0 (18.6–40.4)	43.9 (26.4–57.0)	107.4 (63.7–140.2)
Incidence rate[b]	20.7	54.5	17.1	22.8
Cumulative risk[c]	1:11	1:4	1:13	1:10
RV home care cases[f]				
n, thousands (range)	130.0 (56.1–213.7)	124.2 (55.8–202.2)	175.7 (79.2–285.1)	429.9 (191.1–701.0)
Incidence rate[b]	82.9	218.1	68.2	91.2
Cumulative risk[c]	1:3	1:1	1:3	1:2

RV, rotavirus
[a] Number of rotavirus deaths per year.
[b] Incidence rate per 1000 child-years.
[c] Cumulative under 5-year risk per annual birth cohort.
[d] Number of rotavirus hospitalizations among children aged <5 years per year.
[e] Number of rotavirus outpatient clinic visits per year.
[f] Number of rotavirus home care cases per year.

words, one in every 10 children may visit an outpatient clinic for rotavirus before the age of 5 years, and one in two children will have at least one mild episode of rotavirus diarrhea before the age of 5 years.

4. Discussion

This study presents data on rotavirus epidemiology and burden in three Central Asian countries, which in terms of population and total area represent more than 90% of the region. According to the WHO,[31] Central Asia is a region with high rotavirus morbidity and low mortality. Countries included in this study are located in the same climatic zone and have similar health systems, with a high population coverage (>95%) for primary health care services that include a well-developed immunization system. Routine vaccinations in Central Asia are compulsory and free for the population. In Kazakhstan, the immunization program is fully government-funded, whereas Uzbekistan and Kyrgyzstan are eligible for vaccine support from the GAVI Alliance.

In this study, we summarized long-term data obtained during active hospital-based surveillance, which were organized using an identical study protocol and allowed for comparisons between countries. We estimated 13 381 rotavirus hospitalizations annually in the three countries, with a cumulative hospitalization risk of 1:101 in Uzbekistan, 1:87 in Kazakhstan, and 1:31 in Kyrgyzstan. The risk of rotavirus hospitalization in Central Asia is different from that in other parts of the world. For example, in industrialized countries, the cumulative hospitalization risk for children by the age of 5 years is higher: one in 54 children in Europe[32] and one in 73 children in the USA.[33] The risk of rotavirus hospitalization is usually lower in developing countries, but we believe that for Uzbekistan and Kazakhstan, the true risk for rotavirus hospitalization may be higher than that calculated in our study. This is because these countries do not register all hospitalized cases of gastroenteritis, and due to substantial underreporting, the extent of diarrhea hospitalizations is not captured in the national statistics. The higher hospitalization risk in Kyrgyzstan compared to the other two countries is interesting, as it could not be explained by climatic or geographical differences. It is possible that Kyrgyz hospitals are interested in increasing the number of hospitalized cases since this affects the financing of hospitals by the government.[26] The underestimation was probably the cause of the low average mortality rates that were estimated: 0.27 deaths per 1000 child-years in Kyrgyzstan and 0.25 deaths per 1000 child-years in Uzbekistan. These rates were significantly lower than such estimates presented by Chandran et al. for low and lower-middle income countries (1.38 and 0.53 per 1000 children, respectively).[34] But for Kazakhstan, we estimated a rotavirus mortality (0.04 per 1000) that corresponds to upper-middle income countries (0.069 per 1000).[34]

In Central Asia, rotavirus was detected in an average 26% of stool samples collected from hospitalized patients with diarrhea, with slight variations in detection rates between countries. The highest detection rate was observed in Kazakhstan (30%), followed by Uzbekistan (26%) and Kyrgyzstan (24%). Nonetheless, rotavirus detection rates can fluctuate annually and considering that we only conducted surveillance for 2 years in Kazakhstan, the high rotavirus detection rate there could also be explained by a shorter surveillance period compared to the other two countries. The rotavirus proportion among all causes of gastroenteritis varies by country and over time. According to published reviews, the average detection rate of rotaviruses among children aged less than 5 years increased worldwide from 20% in 1986–1999[1] to 29% in 1990–2004,[3] and to 40% in 2001–2008.[31] Our results could be compared with data provided by Mirzayeva et al.,[35] who reported on rotavirus surveillance conducted in several countries from the WHO European Region using a similar protocol.[36] These data from 2007 show higher rotavirus detection rates by ELISA in the Ukraine (42%), Georgia (40%), and Tajikistan (39%). Another study from Russia[37] reported a rotavirus proportion of 44% established by PCR, which is more sensitive compared to ELISA. Variations in rotavirus proportions cannot only be attributed to economic and climatic differences between these countries, especially because Tajikistan is a low-income country in Central Asia bordering Kyrgyzstan and Uzbekistan. It is likely that hospitalization patterns of patients with diarrhea in each country, as well as deficiencies associated with specimen collection, storage and testing, could have influenced the findings. It is also possible that variations in diarrhea definitions used by hospital physicians could have contributed to lower rotavirus rates in the study countries. Therefore, it is likely that the true rotavirus proportion in countries included in this study is higher than observed.

The peak of rotavirus infection is usually observed between the ages of 9 and 23 months.[1,38,39] In our analysis, we observed a similar age distribution among rotavirus cases in all three countries, with about half the cases (48.4%) infected during the first year of life, and 86.2% were under the age of 2 years. Such rotavirus prevalence in young children is common for developing countries.[38] We also found that 7.0% of all rotavirus cases in Kazakhstan, 5.4% in Kyrgyzstan, and 2.8% in Uzbekistan were in infants under 3 months of age, despite the high breastfeeding rates reported in these countries (95%). Rotavirus infection in infants at that age is fairly uncommon due to protection by maternal antibodies acquired in utero or through breastfeeding.[40,41] However, factors such as malnutrition and other enteric infections can affect a child's immune response and thus contribute to higher rates of rotavirus infection in infancy. At the same time, recent rotavirus vaccine efficacy studies in Africa[12] and Asia[13] have shown low levels of vaccine efficacy due to young age at vaccination and high levels of residual maternal antibodies. The high proportion of positive cases among children under 3 months old in Central Asia could potentially be in favor of more successful vaccination in this region.

The seasonality of rotaviruses varies with increasing longitude, with disease peaks being less pronounced in the equatorial countries.[42–45] Globally, rotavirus is certainly more common in the cooler and drier months[46] of the year and manifests itself more often in the autumn and winter. Seasonality in the Central Asian region shows a common picture for rotaviruses, with a characteristic increase in cases during autumn and winter months.

Our study has a number of limitations. The results presented are only based on data received from sentinel hospitals, which may not be fully representative of the entire country. We did not use a clinical severity score to classify hospitalized cases of diarrhea and assumed that all hospitalized cases were the most severe cases. We did not have the resources to conduct surveillance for cases with moderate or mild diarrhea treated in outpatient clinics or at home, so therefore, the estimated rotavirus burden associated with these cases is based on previous assumptions.[1]

In conclusion, this study presents an epidemiologic picture of rotavirus diseases in Central Asia and illustrates a substantial rotavirus burden that is preventable by the use of rotavirus vaccination. This data, in combination with information on the cost-effectiveness of rotavirus vaccination, may be helpful for national decision-makers who are planning preventive and control measures in the involved countries.

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the personnel at the sentinel hospitals, and the laboratory specialists at the virology laboratories in the involved countries.

Ethical issues: The study protocol was approved by the South Norway Regional Committee of Medical Research and by the national ethics committees of the ministries of health in Kazakhstan, Kyrgyzstan, and Uzbekistan. Informed consent was obtained from parents of all included children.

Conflict of interest: No competing interest declared.

References

1. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003;**9**:565–72.
2. Parashar UD, Gibson CJ, Bresse JS, Glass RI. Rotavirus and severe childhood diarrhea. *Emerg Infect Dis* 2006;**12**:304–6.
3. Parashar UD, Burton A, Lanata C, Boschi-Pinto C, Shibuya K, Steele D, et al. Global mortality associated with rotavirus disease among children in 2004. *J Infect Dis* 2009;**200**(Suppl 1):S9–15.
4. Linhares AC, Bresee JS. Rotavirus vaccines and vaccination in Latin America. *Rev Panam Salud Publica* 2000;**8**:305–31.
5. Anderson EJ, Weber SG. Rotavirus infection in adults. *Lancet Infect Dis* 2004;**4**:91–9.
6. Glass RI, Bresee J, Jiang B, Gentsch J, Ando T, Fankhauser R, et al. Gastroenteritis viruses: an overview. *Novartis Found Symp* 2001;**238**:5–19. discussion 19–25.
7. Kilgore PE, Holman RC, Clarke MJ, Glass RI. Trends of diarrheal disease—associated mortality in US children, 1968 through 1991. *JAMA* 1995;**274**:1143–8.
8. Mrukowicz J, Szajewska H, Vesikari T. Options for the prevention of rotavirus disease other than vaccination. *J Pediatr Gastroenterol Nutr* 2008;**46**(Suppl 2):S32–7.
9. Tate JE, Patel MM, Steele AD, Gentsch JR, Payne DC, Cortese MM, et al. Global impact of rotavirus vaccines. *Expert Rev Vaccines* 2010;**9**:395–407.
10. Vesikari T, Itzler R, Matson DO, Santosham M, Christie CD, Coia M, et al. Efficacy of a pentavalent rotavirus vaccine in reducing rotavirus-associated health care utilization across three regions (11 countries). *Int J Infect Dis* 2007;**11**(Suppl 2):S29–35.
11. Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. *Lancet* 2007;**370**:1757–63.
12. Armah GE, Sow SO, Breiman RF, Dallas MJ, Tapia MD, Feikin DR, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in sub-Saharan Africa: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010;**376**:606–14.
13. Zaman K, Dang DA, Victor JC, Shin S, Yunus M, Dallas MJ, et al. Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010;**376**:615–23.
14. Clark HF, Lawley D, Mallette LA, DiNubile MJ, Hodinka RL. Decline in cases of rotavirus gastroenteritis presenting to The Children's Hospital of Philadelphia after introduction of a pentavalent rotavirus vaccine. *Clin Vaccine Immunol* 2009;**16**:382–6.
15. Paulke-Korinek M, Rendi-Wagner P, Kundi M, Kronik R, Kollaritsch H. Universal mass vaccination against rotavirus gastroenteritis: impact on hospitalization rates in Austrian children. *Pediatr Infect Dis J* 2010;**29**:319–23.
16. Patel M, Pedreira C, De Oliveira LH, Tate J, Orozco M, Mercado J, et al. Association between pentavalent rotavirus vaccine and severe rotavirus diarrhea among children in Nicaragua. *JAMA* 2009;**301**:2243–51.
17. World Health, Organization. Meeting of the immunization Strategic Advisory Group of Experts, April 2009—conclusions and recommendations. *Wkly Epidemiol Rec* 2009;**84**:213–36.
18. World Health Organization. Mortality data. Geneva: WHO; 2010. Available at: www.who.int/healthinfo/statistics/mortality/en/ (accessed October 2010).
19. UNICEF. Statistics: Kazakhstan. UNICEF; December 2009. Available at: http://www.unicef.org/infobycountry/kazakhstan_statistics.html (accessed October 2010).
20. UNICEF. Statistics: Uzbekistan. UNICEF; December 2009. Available at: http://www.unicef.org/infobycountry/uzbekistan_statistics.html (accessed October 2010).
21. UNICEF. Statistics: Kyrgyzstan. UNICEF; December 2009. Available at: http://www.unicef.org/infobycountry/kyrgyzstan_statistics.html (accessed October 2010).
22. The World Bank. Country classifications 2010. Washington DC: The World Bank; 2010. Available at: http://data.worldbank.org/about/country-classifications (accessed October 2010).
23. Global Alliance for Vaccines and Immunization. Available at: http://www.gavialliance.org/resources/Rotavirus_vaccine_expression_of_interest_letter.doc (accessed November 2010).
24. WHO/UNICEF. Review of national immunization coverage 1980–2008: Kazakhstan. Geneva: WHO; 2009. Available at: http://www.who.int/immunization_monitoring/data/kaz.pdf (accessed July 2009).
25. UNICEF. The State of the world's children 2008. UNICEF; 2008. Available at: http://www.unicef.org/sowc08/statistics/tables.php (accessed October 2010).
26. Flem ET, Kasymbekova KT, Vainio K, Gentsch J, Abdikarimov ST, Glass RI, et al. Rotavirus infection in hospitalized children and estimates of disease burden in Kyrgyzstan, 2005-2007. *Vaccine* 2009;**27**(Suppl 5):F35–9.
27. Flem ET, Musabaev E, Juraev R, Kerin T, Gentsch J, Glass RI, et al. Rotavirus gastroenteritis in Uzbekistan: implications for vaccine policy in central Asia. *J Infect Dis* 2009;**200**(Suppl 1):S154–9.
28. Bines J, Bresee J, Ivanoff B, Steele D. Generic protocol for population-based surveillance to define the epidemiology and the incidence of intussusception among children in developing countries. Geneva, Switzerland: WHO Immunization. *Vaccines and Biologicals;* 2007;32.
29. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet* 2010;**375**:1969–87.
30. Parashar UD, Bresee JS, Glass RI. The global burden of diarrhoeal disease in children. *Bull World Health Organ* 2003;**81**:236.
31. Centers for Disease Control and Prevention (CDC). Rotavirus surveillance—worldwide, 2001-2008. MMWR Morb Mortal Wkly Rep 2008;57:1255-7.
32. Soriano-Gabarro M, Mrukowicz J, Vesikari T, Verstraeten T. Burden of rotavirus disease in European Union countries. *Pediatr Infect Dis J* 2006;**25**(1 Suppl):S7–11.
33. Parashar UD, Holman RC, Clarke MJ, Bresee JS, Glass RI. Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. *J Infect Dis* 1998;**177**:13–7.
34. Chandran A, Fitzwater S, Zhen A, Santosham M. Prevention of rotavirus gastroenteritis in infants and children: rotavirus vaccine safety, efficacy, and potential impact of vaccines. *Biologics* 2010;**4**:213–29.
35. Mirzayeva R, Cortese MM, Mosina L, Biellik R, Lobanov A, Chernyshova L, et al. Rotavirus burden among children in the newly independent states of the former Union of Soviet Socialist Republics: literature review and first-year results from the rotavirus surveillance network. *J Infect Dis* 2009;**200**(Suppl 1):S203–14.
36. World Health Organization. Generic protocol for (i) hospital-based surveillance to estimate the burden of rotavirus gastroenteritis in children and (ii) a community-based survey on utilization of health care services for gastroenteritis in children. Field test version. WHO/V&B/02.15. Geneva: WHO; 2002. Available at: http://www.who.int/vaccines-documents/DoxGen/H3DoxList.htm (accessed March 2004).
37. Podkolzin AT, Fenske EB, Abramycheva NY, Shipulin GA, Sagalova OI, Mazepa VN, et al. Hospital-based surveillance of rotavirus and other viral agents of diarrhea in children and adults in Russia, 2005-2007. *J Infect Dis* 2009;**200**(Suppl 1):S228–33.
38. Bresee JS, Glass RI, Ivanoff B, Gentsch JR. Current status and future priorities for rotavirus vaccine development, evaluation and implementation in developing countries. *Vaccine* 1999;**17**:2207–22.
39. Clark B, McKendrick M. A review of viral gastroenteritis. *Curr Opin Infect Dis* 2004;**17**:461–9.
40. Misra S, Sabui TK, Basu S, Pal N. A prospective study of rotavirus diarrhea in children under 1 year of age. *Clin Pediatr (Phila)* 2007;**46**:683–8.
41. Duffy LC, Byers TE, Riepenhoff-Talty M, La Scolea LJ, Zielezny M, Ogra PL. The effects of infant feeding on rotavirus-induced gastroenteritis: a prospective study. *Am J Public Health* 1986;**76**:259–63.
42. Espejo RT, Calderon E, Gonzalez N, Salomon A, Martuscelli A, Romero P. Presence of two distinct types of rotavirus in infants and young children hospitalized with acute gastroenteritis in Mexico City, 1977. *J Infect Dis* 1979;**139**:474–7.
43. Yap KL, Sabil D, Muthu PA. Human rotavirus infection in Malaysia. III. A one year survey on the prevalence of rotavirus enteritis in children. *Southeast Asian J Trop Med Public Health* 1983;**14**:467–9.
44. Hashizume M, Armstrong B, Wagatsuma Y, Faruque AS, Hayashi T, Sack DA. Rotavirus infections and climatic variability in Dhaka, Bangladesh: a time-series analysis. *Epidemiol Infect* 2008;**136**:1281–9.
45. D'Souza RM, Hall G, Becker NG. Climatic factors associated with hospitalizations for rotavirus diarrhoea in children under 5 years of age. *Epidemiol Infect* 2008;**136**:56–64.
46. Cook SM, Glass RI, LeBaron CW, Ho MS. Global seasonality of rotavirus infections. *Bull World Health Organ* 1990;**68**:171–7.